IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AFFYMETRIX, INC., Plaintiff/Counter-Defendant, v. ILLUMINA, INC., Defendant/Counter-Plaintiff.	C.A. No. 04-901-JJF **REDACTED VERSION**

AFFYMETRIX, INC.'S CLAIM CONSTRUCTION BRIEF

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TABLE OF CONTENTS

Page

TABLE OF CITATIONS iii

INTRODUCTION 1

BACKGROUND 1

A. The Basics of DNA 1

B. DNA Microarrays 4

C. The Patents-in-suit 5

ARGUMENT 7

I. THE LAW OF CLAIM CONSTRUCTION 7

II. SUMMARY OF ARGUMENTS 9

III. THE PROPER CONSTRUCTION OF THE '432 PATENT 10

1. "said beads being coded with an encoding system" 10

2. "target specific sequence" 13

IV. THE PROPER CONSTRUCTION OF THE '243 PATENT 15

1. "substrate" 15

2. "target nucleic acids" 18

V. THE PROPER CONSTRUCTION OF THE '531 PATENT 21

1. "probe array" 21

2. "arranged in a spacially defined and physically addressable manner" 23

VI. THE PROPER CONSTRUCTION OF THE '365 PATENT 25

1. "biological polymers immobilized on a surface" 26

2. "housing" 28

VII. THE PROPER CONSTRUCTION OF THE '716 PATENT 29

1. "probe" 30

TABLE OF CONTENTS (continued)

Page

2. "probe intensity" 31

3. "corresponding to probe intensities for a plurality of nucleic acid probes" 34

4. "indicating an extent of hybridization" 35

5. "comparison of said plurality of probe intensities to each other" 36

6. "generates a base call identifying said unknown base" 37

7. "generates a base call . . . according to results of said comparison and said sequences of said nucleic acid probes" 39

CONCLUSION 40

TABLE OF CITATIONS

Page(s)

Cases

CollegeNet, Inc. v. ApplyYourself, Inc.,
418 F.3d 1225 (Fed. Cir. 2005) 8, 33

Electro Med. Sys., S.A. v. Cooper Life Sciences, Inc.,
34 F.3d 1048 (Fed. Cir. 1994) 18

Liquid Dynamics Corp. v. Vaughan Co.,
355 F.3d 1361 (Fed. Cir. 2004) 27, 29, 37

Markman v. Westview Instruments, Inc.,
52 F.3d 967 (Fed. Cir. 1995) 7

Middleton, Inc. v. Minnesota Mining & Mfg. Co.,
311 F.3d 1384 (Fed. Cir. 2002) 8, 23, 28

Pfizer, Inc. v. Teva Pharm. USA, Inc.,
429 F.3d 1364 (Fed. Cir. 2005) ..... passim

Phillips v. AWH Corp.,
415 F.3d 1303 (Fed. Cir. 2005) ..... passim

RF Delaware, Inc. v. Pacific Keystone Techs., Inc.,
326 F.3d 1255 (Fed. Cir. 2003) 25

Sandisk Corp. v. Memorex Prods., Inc.,
415 F.3d 1278 (Fed. Cir. 2005) 8

Vitronics Corp. v. Conceptronic, Inc.,
90 F.3d 1576 (Fed. Cir. 1996) 7, 8, 15, 16

INTRODUCTION

Affymetrix, Inc.'s ("Affymetrix") U.S. Patent Nos. 5,545,531, 5,795,716, 6,355,432, 6,399,365, and 6,646,243 (collectively, the "patents-in-suit")[1] claim inventions related to microarrays and associated technology for use in genetic analysis. Affymetrix asserts that Illumina, Inc. ("Illumina") infringes the patents-in-suit by making and selling microarrays and related products. Pursuant to the Court's direction, the parties have exchanged written proposals regarding the construction of disputed claim terms. Affymetrix proposed that five terms from two patents needed to be construed. (*See* Ex. 1.) Illumina proposed that eleven terms from all five patents needed to be construed. (*See* Ex. 2.) Affymetrix then responded to the terms Illumina had selected for construction. (*See* Ex. 3.) The parties agreed on the construction of one term, leaving fifteen terms in dispute. Two days before this brief was due, Illumina changed its construction of two of the terms. (*See* Ex. 4.) For the Court's convenience, Affymetrix has attached a chart detailing the parties' respective constructions. (*See* Ex. 5.)

Set forth below is Affymetrix's position on the proper interpretation of the disputed terms.

BACKGROUND

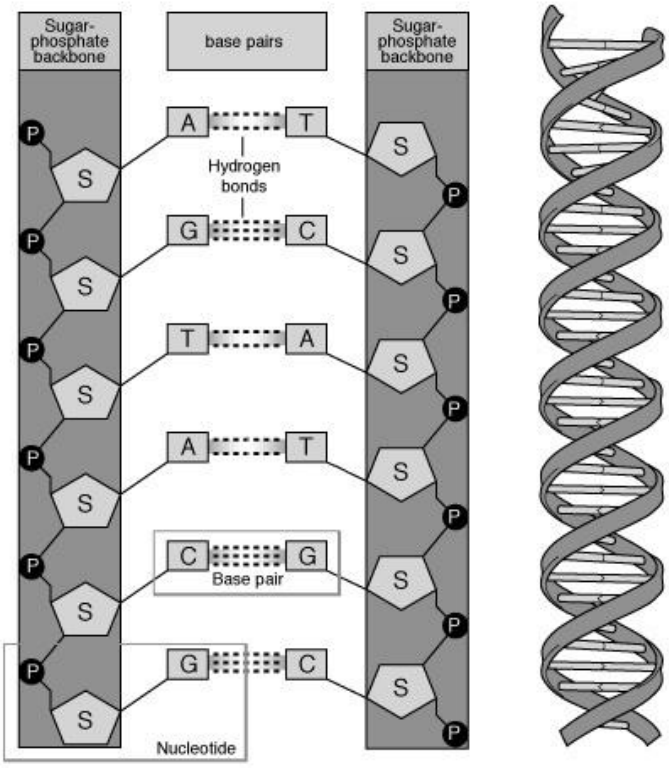
A. The Basics of DNA

The genetic material of most organisms is a template which encodes the information that determines the physical and physiological characteristics of that organism. For an organism to survive from generation to generation, its genetic material must be passed on accurately. The basic building block of all living organisms is the cell. This is true of the simplest "prokaryote" (for example, a bacterium containing essentially one cell type) to the most complex "eukaryote"

[1] After expert evaluation of Illumina's software source code, Affymetrix has elected to dismiss U.S. Patent No. 6,607,887 from this lawsuit.

(such as humans, containing many thousands of different cell types). With few exceptions, each of an organism's cells contains a complete copy of the identical genetic information or material. This complete copy is often referred to as the "genome" of the given organism.

The genome is encoded by the chemical structure of deoxyribonucleic acid ("DNA"). DNA is a double-stranded molecule with two complementary chains running in opposite directions. Each strand of the DNA is a chain of molecules ("nucleotides") with three parts: (1) a phosphate, (2) a sugar, and (3) one of four possible bases. The structure of each nucleotide is constant except for variance of four different bases: adenine ("A"), cytosine ("C"), guanine ("G"), and thymine ("T").[2] The "backbones" of each strand are the phosphate and sugar molecules. Reaching across from these two backbones, the two strands meet in the middle and are connected by "base-pairing." The base A binds only to T (and vice versa) while C binds only to G (and vice versa). The formation of base-pairs between bases on the two opposite strands causes the two strands to coil around each other into the familiar double-helix structure (pictured above), first articulated by James Watson and Francis Crick in 1953.



[2] In the related chemical ribonucleic acid ("RNA"), uracil ("U") takes the place of T.

Complementary base pairing (*i.e.*, A/T and G/C base pairing between strands) makes DNA suitable for carrying genetic information as one strand of DNA can act as a template to direct synthesis of a complementary strand and, thus, copy and pass on the "code" to the next generation of cells. Double-stranded nucleic acid complexes can separate (or "denature") and recombine (or "renature") over a variety of conditions. Two single strands of DNA containing complementary base sequences can come together such that the specific pairing of bases takes place between the complementary strands, and hence double-stranded DNA is formed. This process is referred to as "hybridization." The double-stranded product may be referred to as a "hybrid" or a "duplex." A single-stranded chain of nucleotides may be referred to as a "polynucleotide" or an "oligonucleotide."

Variations in DNA sequences occur in the genomes of different individuals of the same species. These changes or mutations may or may not affect the functioning of a given gene. If one base in a DNA sequence is changed, this is known as a point mutation or single nucleotide polymorphism ("SNP"). The impact of this single changed base or SNP will vary significantly. It may have no effect at all. On the other hand, SNPs may be responsible for many inheritable differences between individuals and SNP variation may indicate predisposition to a disease or may even cause disease.

Inheritance of traits is accomplished by the passing of genetic material via the sex cells from generation to generation. But even after an organism's genetic makeup is determined, its genes will function in different ways. Gene expression is the process by which the instructions in genes are converted to messenger RNA ("mRNA"), which directs protein synthesis. The expression of genetic materials from our genome often varies greatly depending on conditions, such as diet, stress, and so on. Disease also significantly alters the expression of many genes.

Thus, it is useful for scientists to research both (1) the difference in the genetic makeup of individual organisms (a practice broadly described as "genotyping") and (2) the expression of an organism's genes under different conditions, known as "gene expression monitoring."

B. DNA Microarrays

DNA microarrays use the phenomenon of hybridization to discover information about a sample of genetic material. DNA microarray technology involves the attachment of many known sequences of single-stranded DNA on a support (or substrate) at locations that can be associated with the sequences (either during or after attachment). Substrates include slides or other surfaces made of glass or other materials, fibers of glass or other materials, beads, or various combinations of the foregoing (*e.g.*, beads on a glass slide). The substrates can have various surface features (*e.g.*, the surface can be etched with wells or channels, the basic substrate can be coated with a gel or other substance, the substrate or covering can be porous or non-porous, *etc.*).

The array of known sequences is then used to query a sample of DNA (or RNA) molecules using hybridization. Depending on the goal of the researcher, many different biochemistry techniques may be used to prepare the sample materials for hybridization to the array, including, for example, amplification/fragmentation of the sample material or ligation (or joining together) of the sample sequence with another sequence, all through the use of various enzymes or chemicals. Likewise, various techniques can be used to generate a detectable signal (usually optical) where hybridization has occurred. The most common technique is to incorporate a fluorescent label (in one or more colors) that can be detected to indicate where hybridization has occurred. Examining the signals associated with hybridization at different locations on the array allows a scientist to determine whether a particular nucleic acid sequence is present or absent in a given sample.

Affymetrix pioneered the development of DNA microarrays and related technology. Affymetrix's GeneChip® arrays have revolutionized genetic analysis and research. Researchers have published thousands of peer-reviewed papers based on Affymetrix's technology. Affymetrix's achievements have also been recognized with many distinguished scientific awards, including Distinguished Inventor of the Year (1993), The Association for Laboratory Automation Achievement Award (1998), the Takeda Foundation Award (2002), the Association of Biomedical Research Facilities Award for Outstanding Contributions to Biomolecular Technologies (2005), and the Edwin F. Ullman Award from the American Association for Clinical Chemistry (2005).

In the course of developing DNA microarray technology, Affymetrix made substantial investments in research and development to establish a position of technological leadership. Affymetrix owns valuable and wide-ranging intellectual property rights in this area to protect its significant investment, including over 350 issued U.S. patents and over 500 pending U.S. patent applications relating to all aspects and forms of microarray technology.

C. The Patents-in-suit

The five patents-in-suit cover a wide-range of microarrays and associated technology. U.S. Patent Nos. 6,355,432 (the "'432 patent") and 6,646,243 (the "'243 patent") claim priority to applications filed in 1990, the early days of Affymax (the predecessor to Affymetrix). Each relates to the use of beads in the analysis of nucleic acids. U.S. Patent Nos. 5,545,531 (the "'531 patent") and 6,399,365 (the "'365 patent") claim priority to applications filed in 1995 and 1994, respectively, a time in which Affymetrix was entering a commercialization phase. The '531 patent relates to a plurality of microarrays attached to a body containing wells. The '365 patent relates to packages for hybridization and microarrays including a bar code. Finally, the application leading to U.S. Patent No. 5,795,716 (the "'716 patent") was filed in 1994 and relates

to computer programs for making base calls. Each of the patents-in-suit arises from a separate patent family. They are all owned by Affymetrix but are otherwise not related.

The '432 patent issued on March 12, 2002, and is entitled "Products for detecting nucleic acids." (*See* Ex. 6.) The '432 patent claims a plurality of beads with oligonucleotides attached. The beads in the '432 patent are encoded in some fashion so that the sequence of the oligonucleotides attached to each bead can be determined. Affymetrix has asserted claims 2, 5, 8-10, 21, and 22 of the '432 patent.

The '243 patent issued on November 11, 2003, and is entitled "Nucleic acid reading and analysis system." (*See* Ex. 7.) The '243 patent claims apparatuses and methods for scanning DNA microarrays consisting of beads with nucleic acids attached. Affymetrix has asserted claims 14-16, 19, 20, 22, 24, 26, 35, 36, 39, 40, 43, 52, and 53 of the '243 patent.

The '531 patent issued on August 13, 1996, and is entitled "Methods for making a device for concurrently processing multiple biological chip assays." (*See* Ex. 8.) The '531 patent covers methods of making a plurality of microarrays on a support and attaching that support to a body that includes wells so that the microarrays are exposed to the wells or forming test wells on the support itself. The exposure of a microarray to a well allows for a sample (of, for example, DNA) in that well to be hybridized to the associated microarray. A plurality of microarrays on a support permits the hybridization of many different samples (each contained in a separate well) in a single experiment. Affymetrix has asserted claims 1-4 of the '531 patent.

The '365 patent issued on June 4, 2002, and is entitled "Bioarray chip reaction apparatus and its manufacture." (*See* Ex. 9.) The asserted claims of the '365 patent are directed primarily to hybridization packages for microarrays or microarrays themselves and a bar code. Affymetrix has asserted claims 17, 18, 21, 22, 24, 27, 28, 35-37, 41, 43-45, 55, and 58 of the '365 patent.

The '716 patent issued on August 18, 1998, and is entitled "Computer-aided visualization and analysis system for sequence evaluation." (*See* Ex. 10.) The '716 patent claims computer programs and systems that are used to compare probe intensities to generate a "base call."[3] Affymetrix has asserted claims 1, 2, 5, 6, 9, and 10 of the '716 patent.

ARGUMENT

I. THE LAW OF CLAIM CONSTRUCTION

Patent claim construction is an issue of law. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995). The words of the claim define the scope of the patented invention. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (*en banc*); *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). In construing terms used in a patent claim, the Court should give primary importance to the intrinsic record – that is, the claims themselves, the specification, and the prosecution history. *Phillips*, 415 F.3d at 1312-19.

Claim terms should generally be given their plain and ordinary meaning, as understood by one of ordinary skill in the art. *Id.* at 1312 ("We have frequently stated that the words of a claim are generally given their ordinary and customary meaning.") (internal quotation marks omitted). When the ordinary meaning of a claim term is readily apparent, "claim construction in such cases involves little more than the application of the widely accepted meaning of commonly understood words." *Id.* at 1314. When the meaning of a claim term is not immediately apparent,

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[3] The '716 patent was the subject of a claim construction order in an earlier case, *Affymetrix, Inc. v. Hyseq, Inc. et al.*, Case No. C 99-21163 JF (N.D. Cal.). (*See* Ex. 11.)

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Affymetrix has attached its opening claim construction brief from the *Hyseq* case as an exhibit should the Court wish to review it. (Ex. 12.) Illumina has not argued in this case that the terms of the '716 patent are means-plus-function terms.

the meaning should be determined with reference to the words of the claims themselves, the specification, the prosecution history, and, perhaps less importantly, extrinsic evidence. *Id.*

The claims themselves can provide substantial guidance as to the meaning of particular claim terms. For example, the context in which a term is used in a claim or differences among claims can inform the interpretation of a particular term. *Phillips*, 415 F.3d at 1314-15.

The specification also informs the meaning of claim terms. "The specification acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication." *Vitronics*, 90 F.3d at 1582. In such cases, "the inventor's lexicography governs." *Phillips*, 415 F.3d at 1316. The specification can also indicate an intentional disclaimer, or disavowal, of claim scope by the inventor. *Id.* The Federal Circuit has stated, however, that any such disavowal must be clear and unambiguous. *See, e.g., Middleton, Inc. v. Minnesota Mining & Mfg. Co.*, 311 F.3d 1384, 1388 (Fed. Cir. 2002).

While one should consult the patent specification when construing claim terms, it is also critical not to import limitations from the specification into the claims. Because it is the language of the claim, and not the examples or embodiments described in the specification, that defines the scope of the invention, the Federal Circuit has consistently warned about this form of legal error. *See, e.g., CollegeNet, Inc. v. ApplyYourself, Inc.*, 418 F.3d 1225, 1231 (Fed. Cir. 2005) ("In examining the specification for proper context, however, this court will not at any time import limitations from the specification into the claims."). Similarly, "a claim construction that excludes a preferred embodiment . . . is rarely, if ever, correct." *Pfizer, Inc. v. Teva Pharm. USA, Inc.*, 429 F.3d 1364, 1374 (Fed. Cir. 2005) (internal quotation marks and citations omitted); *Sandisk Corp. v. Memorex Prods., Inc.*, 415 F.3d 1278, 1285 (Fed. Cir. 2005) (reversing claim construction because it excluded a preferred embodiment).

While less useful than the specification for claim construction purposes, the prosecution history "can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." *Phillips*, 415 F.3d at 1317. The Federal Circuit has cautioned, however, that the prosecution history often lacks the clarity of the specification. *Id.*

II. SUMMARY OF ARGUMENTS

Affymetrix's proposed claim constructions are consistent with the teachings of the *Phillips* court. The ordinary meaning of these claim terms to one of skill in the art is clear in light of the relevant specification. Illumina, by contrast, follows the accused infringer's game plan of creating additional limitations that are not part of the claims to manufacture non-infringement arguments. Indeed, several of Illumina's constructions include a naked non-infringement argument in a parenthetical within the proposed construction. These extra limitations are neither supported by the intrinsic evidence nor by the law of claim construction.

While the parties have many disagreements over the disputed terms, Illumina's main claim construction errors can be broken down into the following categories:

- Illumina attempts to limit the substrate or surface of the claimed microarrays to a "single surface." In doing so, Illumina ignores that no such limitation appears in the claims or even in the specifications. Moreover, several of the patent-in-suit specifications expressly discuss the use of a substrate consisting of multiple surfaces, including beads alone or in combination with other materials.

- Illumina attempts to limit the substrate of the claimed microarrays to a surface on which polymers are synthesized rather than attached after synthesis. Once again, this limitation does not appear in any of the asserted claims. The patents-in-suit provide examples where a pre-formed polymer is attached to the substrate.

- Illumina attempts to limit the patents-in-suit to hybridization of the probes to a target "at the sequence to be determined." Neither the claims themselves nor the specification are so limited. Indeed, the patents-in-suit provide examples where a

> polymer sequence other than the ultimate sequence to be determined is hybridized to the known probe sequence.

While attempting to add limitations that do not appear in the claims, Illumina ignores express definitions of disputed terms provided in the specification, excludes preferred embodiments, and selectively relies on portions of the specifications while disregarding others. In short, Illumina seeks to use the claim construction process to assert its non-infringement arguments.

III. THE PROPER CONSTRUCTION OF THE '432 PATENT

The two disputed terms (with emphasis added) in the '432 patent can be found in claim 1:

> A collection of beads comprising a plurality of beads which have binding polymers of different target specific sequence attached thereto; ***said beads being coded with an encoding system*** whereby the ***target specific sequence*** of the polymer attached to the beads can be identified.

(Ex. 6.) Each of the claims of the '432 patent asserted by Affymetrix against Illumina depends from claim 1. The claims relate to a plurality of beads with polymers attached and a system by which one can determine which polymer is attached to which bead. Affymetrix proposes the following claim constructions for the disputed terms of the '432 patent.

1. "said beads being coded with an encoding system"

Affymetrix's proposed construction: "said beads being distinguishable one bead from another"

Illumina's proposed construction: "a property associated with a bead (separate from the binding polymer) that can be used to distinguish one bead from another"

Illumina's April 3 construction: "said beads having a property associated with each bead (separate from the binding polymer) that can be used to distinguish one bead from another"

This phrase is simple to understand and should be construed according to its plain and ordinary meaning – it requires that the beads be distinguishable from one another.[4] As made clear by the claim itself, the purpose of the encoding system is to allow identification of which polymer is attached to which bead. The claim does not limit what can serve as an "encoding system." Therefore, the phrase "said beads being coded with an encoding system" means "said beads being distinguishable one bead from another."

This construction is consistent with the '432 patent's specification, which describes beads being coded with an encoding system in very general terms:

> After the relatively small number of beads which have bound the target have been collected, the encoding scheme may be read off to determine the specificity of the reagent on the bead. An encoding system may include a magnetic system, a shape encoding system, a color encoding system, or a combination of any of these, ***or any other encoding system.***

(Ex. 6, col. 21, lines 58-64 (emphasis added).) There is nothing in the specification or the claims themselves to suggest that the inventors intended to limit the encoding system in any way – it merely serves as a means to distinguish one bead from another.

Illumina's proposed construction, by contrast, inserts a naked non-infringement argument into a parenthetical – "separate from the binding polymer" – and disregards the teaching of the specification. As an initial matter, there is nothing in the claim to suggest that the encoding system must be separate from the binding polymer. *See Phillips*, 415 F.3d at 1314 ("[T]he claims themselves provide substantial guidance as to the meaning of particular claim terms."). So long as the binding polymer attached to the bead allowed one to distinguish one bead from another, the binding polymer could serve as the encoding system. As one example, an

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[4] Illumina proposed that the entire phrase be construed. It may be more helpful and appropriate to construe "encoding system" as "a means for distinguishing one bead from another."

oligonucleotide attached to a bead could be both a "binding polymer" and an "encoding system" – by hybridizing a known sequence to the oligonucleotide, one could determine which oligonucleotide is attached to which bead.[5] That same oligonucleotide attached to the bead could then be used as the "binding polymer" referenced in the claim.

Indeed, the specification discloses such an encoding system:

> In addition, ***polymers may be used*** as markers or for information containing molecules ***to encode information*** . . . . Whether the resolution is absolute or less so, ***the concept of coding information on molecules such as nucleic acids***, which can be amplified and later ***decoded***, may be a very useful and important application.

(Ex. 6, col. 58, lines 11-40 (emphasis added).) As noted above, the specification also discloses the use of "any other encoding system" with beads. Clearly, one of these "other encoding system[s]" contemplated by the inventors was the use of a binding polymer, including the specific example of a nucleic acid. Illumina's attempt to exclude this encoding system – when it is expressly described in the specification – violates the basic principles of claim construction. *See Pfizer*, 429 F.3d at 1374 ("A claim construction that excludes a preferred embodiment . . . is rarely, if ever, correct.").

Illumina's proposed construction – "a property associated with each bead" – also suggests that the encoding system must be intrinsic to the bead. The patent describes encoding schemes that can be either intrinsic or extrinsic to the bead. For example, the color of the bead can be a property of the bead itself or could be added to the bead through the use of a fluorescent

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[5] During the discovery process in this case, Illumina's witnesses,

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Illumina's publications describe the process of identifying which bead is in each location as "decoding" the array. (*See* Ex. 15.) Illumina's claim construction position is directly at odds with these previous statements.

marker on the exterior of the bead. As we have seen, the patent also describes the use of encoding systems that are clearly not intrinsic to the bead – such as the use of a molecule as a marker. For this further reason, Illumina's proposed construction is unsupportable.

2. "target specific sequence"

Affymetrix's proposed construction: "a known polymer sequence that has affinity for another sequence"

Illumina's proposed construction: "a known sequence of a polymer that binds with specificity to the target at the sequence to be determined"

The beads claimed in the '432 patent have binding polymers of different "target specific sequence" attached. The term "target specific sequence" refers to the polymers attached to the beads (or probes) having a sequence that has affinity (or specificity) for a polymer of some other sequence (or target). The plain and ordinary meaning of "target" is a molecule that has an affinity for a given probe.[6] Put another way, the "target" is what one intends to bind to the polymer attached to the bead (which can be thought of as the "probe"). Therefore, a "target specific sequence" is a known sequence that has affinity for the target.

The specification of the '432 patent does not require that the binding polymer be specific for any particular type of target. In one illustration, the polymers attached to the support are designed to be specific for all possible sequences of that length in a sample of DNA of unknown sequence to be determined (called a "sequencing" application). (Ex. 6, col. 22, lines 6-23.) In another illustration, the polymers attached to the support are oligonucleotides designed to be specific for their complementary sequences which are known and are used as "tag" sequences attached to other molecules so that those molecules can be directed to the surface of the support

[6] Indeed, several of the other patents-in-suit define target as "a molecule that has an affinity for a given probe." *See* '365 patent (Ex. 9, col. 4, lines 15-16); '531 patent (Ex. 8, col. 3, lines 49-50); '243 patent (Ex. 7, col. 6, lines 28-29 (defining "receptor" as "a molecule that has an affinity for a given ligand" – where receptor and ligand are used synonymously with target and probe)).

at a known location and used in a subsequent assay. (Ex. 6, col. 27, lines 36-56; *see also* col. 33, line 66 to col. 34, line 22.) In the latter example, the known polymer sequence has affinity for another sequence – the "tag" sequence – that is ***not*** the sequence to be determined in the experiment. Rather, the tag serves as a marker for the sequence of interest.

Both the claims and the specification of the '432 patent make clear that the term "target specific sequence" should be interpreted broadly to mean "a known polymer sequence that has affinity for another sequence." The inventors did not express any intent to limit the term to a particular type of molecule or application.

Illumina's proposed construction adds a limitation – "at the sequence to be determined" – that does not appear in the claims and is directly contradicted by the specification. This construction would limit the invention to the use of binding polymers on the bead that bind with specificity ***only at the sequence to be determined***. As we have seen, however, the '432 patent discloses the use of binding polymers on a support that are specific for sequences ***other than those to be determined***, *e.g.*, tag sequences that have been added to a binding polymer.

In the "tag" examples discussed above, the oligonucleotides (or binding polymers) attached to the support are specific for the complementary (or tag) oligonucleotides that have been attached to other molecules (such as an antibody) that are to be used subsequently as probes. The tag oligonucleotides bind to the oligonucleotides attached to the support, thereby immobilizing the "tagged" molecule at a known location. That molecule is then available to serve as a probe to query the ultimate sequence of interest. The important thing, however, is that the binding polymer attached to the support was ***not*** specific for the "sequence to be determined" – it was specific for a ***known*** tag sequence used to direct another molecule to a location. (Ex. 6, col. 27, lines 36-56; col. 33, line 66 to col. 34, line 22.)

Thus, Illumina's proposed construction – which adds the "at the sequence to be determined" limitation – is directly contradicted by the specification. *See Pfizer*, 429 F.3d at 1374 ("A claim construction that excludes a preferred embodiment . . . is rarely, if ever, correct."). Affymetrix's proposed construction, by contrast, is consistent with the intrinsic record and should be adopted. *See Vitronics*, 90 F.3d at 1582.

IV. THE PROPER CONSTRUCTION OF THE '243 PATENT

The two disputed terms (with emphasis added) in the '243 patent can be found in claim 14:

> An apparatus for analyzing nucleic acid binding, comprising:
>
> a ***substrate*** that comprises at least 1000 different spheres, beads, or particles having different species of nucleic acids attached thereto, the area of the substrate containing the at least 1000 spheres, beads, or particles being less than 1 cm2, at least some of the nucleic acids being bound to fluorescently labeled ***target nucleic acids***;
>
> a laser energy source to illuminate the fluorescent labels;
>
> a detector to detect a fluorescent label bound to said target nucleic acids; and
>
> a data collection system for storing fluoresced light intensity.

(Ex. 7.) Claim 14 and its dependent claims are directed to an apparatus for scanning a bead microarray. Other asserted claims in the '243 patent relate to methods for such scanning. Affymetrix proposes the following claim constructions for the disputed terms of the '243 patent.

1. "substrate"

Affymetrix's proposed construction: "a material having a rigid or semi-rigid surface"

Illumina's proposed construction: "material on whose surface polymers are synthesized"

Illumina's April 3 construction: "a material having a rigid or semi-rigid surface on which polymers are synthesized"

The term "substrate" is defined in the '243 patent's glossary as "a material having a rigid or semi-rigid surface." (Ex. 7, col. 7, lines 35-36.) The Federal Circuit is clear that the definition of "substrate" in the patent should control. *See Phillips*, 415 F.3d at 1316 ("In such cases, the inventor's lexicography governs."); *Vitronics*, 90 F.3d at 1582. The remainder of the '243 patent's specification uses the term consistently with this definition.

For example, the inventors stressed that they did not intend to put limits on the material that could serve as a substrate:

> Essentially, any conceivable substrate may be employed in the invention. The substrate may be biological, nonbiological, organic, inorganic, or a combination of any of these, existing as particles, strands, precipitates, gels, sheets, tubing, spheres, containers, capillaries, pads, slices, films, plates, slides, etc. The substrate may have any convenient shape, such as a disc, square, sphere, circle, etc. The substrate is preferably flat but may take on a variety of alternative surface configurations. For example, the substrate may contain raised or depressed regions on which the synthesis takes place. The substrate and its surface preferably form a rigid support on which to carry out the reactions described herein.

(Ex. 7, col. 10, lines 54-66.) The critical characteristic of the substrate is that it includes a rigid or semi-rigid surface sufficient to immobilize the polymer, in this case nucleic acids, for use in the hybridization experiment.

The claim language itself is also consistent with this construction. Claim 14 requires that the substrate comprise, or include, at least 1000 different spheres, beads, or particles. A material having a rigid or semi-rigid surface could certainly have beads attached to its surface as is described in the patent. (Ex. 7, col. 7, lines 41-42 (stating that "small beads may be provided on the surface" of the substrate).)

Illumina's original construction, by contrast, ignored the definition of "substrate" provided in the specification and, instead, tried to manufacture a non-infringement argument by limiting the claims of the '243 patent to a substrate where the nucleic acids are synthesized on

the surface. While Illumina subsequently embraced the definition of substrate as a rigid or semi-rigid material, they maintain their focus on the substrate as the location of synthesis. Neither the law nor the intrinsic evidence supports Illumina's proposed construction.

The starting point for the analysis is the claim itself. *Phillips*, 415 F.3d at 1314. Synthesis of the polymers on the surface of the substrate appears nowhere in claim 14 (or any other claim of the '243 patent). The claim language requires that at least 1000 different spheres, beads, or particles be included as part of the substrate and that the spheres, beads, or particles have nucleic acids attached to them. The claims say nothing about when or where the nucleic acids are synthesized.

In addition to being inconsistent with the claim language, Illumina's proposed construction disregards the definition of "substrate" provided in the patent's glossary. *See Phillips*, 415 F.3d at 1316 (stating that where the specification provides a definition, "the inventor's lexicography governs"). The inventors defined the term to mean "a material having a rigid or semi-rigid surface." (Ex. 7, col. 7, lines 35-36.) This definition does not speak to whether the polymers are synthesized on the surface of the substrate or attached after synthesis. The glossary goes on to discuss that "in ***some embodiments*** it may be desirable to physically separate synthesis regions for different polymers," Ex. 7, col. 7, lines 37-39 (emphasis added), and "[a]ccording to ***other embodiments***, small beads may be provided on the surface which may be released upon completion of the synthesis," Ex. 7, col. 7, lines 40-43 (emphasis added). Therefore, while the inventors did discuss embodiments where synthesis occurred on the surface of the substrate, they made clear that they were doing so only in the context of particular embodiments. *See Electro Med. Sys., S.A. v. Cooper Life Sciences, Inc.*, 34 F.3d 1048, 1054 (Fed. Cir. 1994) ("[P]articular embodiments appearing in a specification will not be read into the claims when the claim language is broader than such embodiments.").

Most tellingly, the '243 patent describes an example that directly contradicts Illumina's proposed construction. Example H discusses the attachment of a ***preformed*** polypeptide sequence, the Leu enkephalin sequence (or "YGGFL"), to the surface of the substrate. (Ex. 7, col. 25, line 62 to col. 26, line 27.) The inventors note that the "method provides for successful coupling of peptides to the surface of the substrate." (Ex. 7, col. 26, line 23-24.) In contrast, the next example discusses monomer-by-monomer synthesis of that same polypeptide sequence on the surface of the substrate. (Ex. 7, col. 26, line 28 to col. 27, line 10.) Thus, the patent provides an example where the synthesis of the polymer occurs ***before*** attachment to the substrate and presents it as an alternative to synthesis on the substrate. *See Pfizer*, 429 F.3d at 1374 ("A claim construction that excludes a preferred embodiment . . . is rarely, if ever, correct.").

After receiving Affymetrix's proposed construction of the term "substrate," Illumina amended its construction on April 3 (two days before the due date for the brief) to reflect the definitional language from the patent, "a material having a rigid or semi-rigid surface," while still attempting to import the limitation of the substrate as the synthesis location. However, Illumina's revised construction makes its error all the more clear: Illumina agrees that the definition of the term should control, but then tacks on a limitation to create a non-infringement argument. There is no support in the '243 patent or the law for Illumina's attempt to amend the definition of the term to suit its purposes.

Affymetrix's proposed construction of "substrate" – "a material having a rigid or semi-rigid surface" – is consistent with the definition of the term in the patent, the claim language, and the specification. Accordingly, Affymetrix's construction should be adopted.

2. <u>"target nucleic acids"</u>

<u>Affymetrix's proposed construction</u>: "nucleic acids that have an affinity for the nucleic acid attached to the bead"

Illumina's proposed construction: "sample nucleic acids with sequence to be determined"

Claim 14 of the '243 patent requires that "at least some of the nucleic acids" attached to the beads are "bound to fluorescently labeled target nucleic acids." The term "target" is not used in the specification of the '243 patent. However, a synonymous term, "receptor," is defined in the glossary as "[a] molecule that has an affinity for a given ligand."[7] (Ex. 7, col. 6, lines 28-29.) Nucleic acids are given as examples of receptors. (Ex. 7, col. 6, line 38; col. 7, lines 5-7.) A "ligand" is defined as "a molecule that is recognized by a particular receptor."[8] (Ex. 7, col. 5, lines 57-58.) Ligands include nucleic acids. (Ex. 7, col. 5, line 64.) Thus, the term "target nucleic acids" should be construed consistently with the definition of "receptor" provided in the '243 patent's specification.

Throughout the specification, "receptor" is used to refer to the molecules that bind to the polymers (or probes) attached to the substrate. (Ex. 7, col. 3, lines 31-51 ("To screen for biological activity, the substrate is exposed to one or more receptors . . . . The receptors are preferably labeled with, for example, a fluorescent marker, radioactive marker, or a labeled antibody reactive with the receptor."); col. 3, line 67 to col. 4, line 4 ("The detection method and apparatus utilize a substrate having a large variety of polymer sequences at known locations on a surface thereof. The substrate is exposed to a fluorescently labeled receptor which binds to one or more of the polymer sequences.").)

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[7] Other patents-in-suit define the term "target" in a very similar manner: "a molecule that has an affinity for a given probe." *See* '365 patent (Ex. 9, col. 4, lines 15-16); '531 patent (Ex. 8, col. 3, lines 49-50). The '365 patent specifically states that a "target" is "sometimes referred to as a receptor." (Ex. 9, col. 4, line 16.)

[8] Other patents-in-suit define "probe" in a nearly identical manner: "a surface-immobilized molecule that is recognized by a particular target and is sometimes referred to as a ligand." *See* '365 patent (Ex. 9, col. 4, lines 4-6). *See also* '531 patent (Ex. 8, col. 3, lines 39-40).

As made clear by claim 14, the "target nucleic acids" are ones that have bound to the nucleic acids attached to the beads. (Ex. 7, col. 30, lines 55-61 ("1000 different spheres, beads, or particles having different species of nucleic acids attached thereto . . . at least some of the nucleic acids being bound to fluorescently labeled target nucleic acids.") The term "target nucleic acids" is used in the claims in the same manner that "receptor" is used in the specification: a molecule that has affinity for a given ligand. In the claims of the '243 patent, the molecule is a nucleic acid and the ligand is the nucleic acid attached to the bead. Therefore, the proper construction of "target nucleic acids" is "nucleic acids that have an affinity for the nucleic acid attached to the bead."

Illumina's proposed construction injects into the claim a limitation – "with sequence to be determined" – that is not supported by the claim language or the specification. This construction is similar to (and flawed for the same reasons as) Illumina's proposed construction of "target specific sequence" in the '432 patent, discussed *supra*. First, nothing in the claim language requires that the "target nucleic acids" be the nucleic acids with "sequence to be determined." Rather, the only requirement is that the target nucleic acids be bound to the nucleic acids attached to the beads. Obviously, there are many types of nucleic acids – such as the "tag" sequences discussed in section III.C.2., *supra* – that can bind to the nucleic acids attached to the beads other than those sequences that are to be determined in the experiment.

Second, Illumina's proposed construction again ignores the definitions found in the specification. As discussed above, the patent defines "receptor" – the equivalent of "target" – broadly as a "molecule that has an affinity for a given ligand," not limited to sequences that are to be determined. The glossary goes on to state that "[r]eceptors may be naturally-occuring [*sic*] or manmade molecules. Also, they can be employed in their unaltered state or as aggregates with other species." (Ex. 7, col. 6, lines 29-31.) Manmade molecules could serve as "tag"

sequences to mark other naturally-occurring molecules. Similarly, the reference to "aggregates with other species" includes the use of target molecules to mark other sequences of interest.

Neither the definition of "receptor" nor the claim language itself indicates any intent to limit the meaning of the term "target nucleic acids." For each of these reasons, Affymetrix's construction of the term should be adopted.

V. THE PROPER CONSTRUCTION OF THE '531 PATENT

The two disputed terms (with emphasis added) in the '531 patent can be found in claim 1:

> A method for making a biological chip plate comprising the steps of:
>
> (a) providing a body comprising a plurality of wells defining spaces;
>
> (b) providing a wafer comprising on its surface a plurality of probe arrays, each ***probe array*** comprising a collection of probes, at least two of which are different, ***arranged in a spacially defined and physically addressable manner***;
>
> (c) attaching the wafer to the body so that the probe arrays are exposed to the spaces of the wells.

(Ex. 8.) As is clear from its ordinary meaning, the claim covers a method for making a plurality of arrays and attaching that plurality to a body including wells. The two disputed terms appear in each of the four claims of the '531 patent. Affymetrix proposes the following constructions for the two disputed terms.

1. "probe array"

Affymetrix's proposed construction: "a collection of surface-immobilized molecules, at least two of which are different, that can be recognized by a particular target"

Illumina's proposed construction: "a collection of probes, at least two of which are different, that are surface-immobilized (chemically linked) to a single surface"

The term "probe array" is made up of two terms, "probe" and "array," that appear in the "Definitions" section of the '531 patent. (Ex. 8 at cols. 3-4.) Therefore, the proper construction of "probe array" must incorporate these definitions. *See Phillips*, 415 F.3d at 1316. The

specification defines "probe" as "a surface-immobilized molecule that can be recognized by a particular target." (Ex. 8 at col. 3, lines 39-40.) "Array" is defined as "[a] collection of probes, at least two of which are different, arranged in a spacially defined and physically addressable manner." (Ex. 8 at col. 4, lines 1-3.)

Affymetrix's proposed construction of "probe array" combines these two definitions and is, therefore, directly supported by the specification. Affymetrix omits the "arranged in a spacially defined and physically addressable manner" portion of the "array" definition because that clause appears after "probe array" in the claims of the '531 (and would, therefore, be duplicative). Affymetrix's proposed construction is also consistent with the discussion of probe arrays in the specification. (*See, e.g.*, Ex 8, col. 1, lines 15-20 ("probes arranged in arrays . . . can be used to determine whether target molecules interact with any of the probes on the chip").)

Illumina's proposed construction attempts to limit the claims of the patents-in-suit to an array with a "single surface" and would require a chemical linkage. This is motivated by Illumina's non-infringement position: namely, that Illumina's BeadArrays include multiple surfaces, with beads attached to an underlying support. The '531 patent, however, does not support Illumina's construction of "probe array" as being limited to "chemical linkage" to a "single surface." Neither the definition of "probe" nor "array" includes any such limitation. In the absence of any express disavowal of claim scope, none should be implied. *See, e.g.*, *Middleton,* 311 F.3d at 1388 (stating that any disavowal must be clear and unambiguous). Indeed, the specification discusses the substrate and its surface in broad, not limiting, terms:

> The substrate is preferably flat but may take on a variety of alternative surface configurations. For example, the substrate may contain raised or depressed regions on which the probes are located . . . . Surfaces on the solid substrate usually, though not always, are composed of the same material as the substrate.

(Ex. 8, col. 9, lines 29-45.) The use of the plural "surfaces" in the above disclosure includes the possibility of more than a single surface.

Similarly, the specification makes clear that what is important is that the probes are immobilized to prevent them from moving during use so that one will know what sequences are where. It is not important that they be "chemically linked" to a "single surface" – rather, so long as the probes are surface-immobilized in some fashion (whether on a single surface, multiple surfaces attached to an underlying support, or some combination), they will be useable in the assay (or experiment). The specification discusses attaching the probes to, for example, a membrane or a resin, which is then in turn attached to the underlying support. (Ex. 8, col. 9, lines 44-50.) There are many ways to immobilize probes – the inventors nowhere indicated an intention to limit their invention to chemically linking probes to a single surface.

Illumina's proposed construction improperly attempts to narrow the invention by ignoring the definitions and other language in the specification. For these reasons, and those discussed above, Affymetrix's construction of "probe array" should be adopted.

2. "arranged in a spacially defined and physically addressable manner"

Affymetrix's proposed construction: "located in a particular location and capable of being accessed"

Illumina's proposed construction: "each probe in an array is placed in a different pre-determined location on the surface"

The probes on the array must be "arranged in a spacially defined and physically addressable manner." With regard to "spacially defined," the ordinary meaning of that term is "located in a particular location." The probes in the arrays claimed by the '531 patent are immobilized at a specific location. (*See, e.g.*, Ex. 8, col. 3, line 39 (defining probe as a "surface-immobilized molecule"); col. 1, line 16 (stating that in an array each probe is associated with a

"specific location").) The purpose of arranging the probes in a "spacially defined" manner is to allow the experimenter to determine, after hybridization, which probes hybridized and, therefore, which sequences complementary to or associated with those probes were present in the sample. (Ex. 8, col. 4, lines 64-66 ("Accordingly, locations at which target(s) bind with complementary probes can be identified by detecting the location of the label.").) The claim language itself and the specification express no preference for ***when*** the specific location of each probe is determined – so long as the location of the probe on the array is defined, whether before or after immobilization, the experimenter can determine whether hybridization took place. (Ex. 8, col. 4, line 66 to col. 5, line 2 ("Through knowledge of the characteristics/sequence of the probe versus location, characteristics of the target can be determined.").)

The probes on the array must also be arranged in a "physically addressable" manner. This term means that the probes are capable of being accessed – that is, the experimenter can access the probes with the target and can determine where binding occurred. (*See, e.g.*, Ex. 8, col. 1, lines 20-24 ("After exposing the array to target molecules under selected test conditions, scanning devices can examine each location in the array and determine whether a target molecule has interacted with the probe at that location."); col. 11, lines 1-4 ("Accordingly, locations at which targets hybridize with complimentary probes can be identified by locating the markers. Based on the locations where hybridization occurs, information regarding the target sequences can be extracted.").) As the specification points out, the "probes are arrayed on a chip in addressable rows and columns," which allows meaningful information to be extracted when a target sample is directed to the probe and a subsequent detection is made at that location. (Ex. 8, col. 10, lines 32-33.)

In short, the phrase "arranged in a spacially defined and physically addressable manner" describes the property of probe arrays that allow those probe arrays to work – one must be able to add a sample to the array and determine which probes have bound to targets.

Illumina's proposed interpretation of this phrase is, once again, an attempt to introduce a non-infringement argument into claim construction. Specifically, Illumina tacks on a limitation – that each probe is placed in a "***pre-determined*** location" – that is neither in the claim nor mandated by the specification. The claim itself says only that the probes must be "arranged" in a "spacially defined and physically addressable manner." There is no requirement that the location of the probe be determined prior to placement. Certainly, probes can be "arranged" in a "spacially defined and physically addressable manner" without knowing ***prior to placement*** the specific location of each probe. One could simply determine the specific location of each probe ***after*** placement and those probes would still be "spacially defined and physically addressable."

Similarly, the specification nowhere evinces an intent on behalf of the inventors to limit their invention to arrays where probes are placed only at pre-determined locations. While the patent does discuss embodiments in which probes on an array are synthesized at known locations, *see, e.g.*, Ex. 8, col. 10, lines 10-15, it is improper to use that written description to limit the claim terms. *See RF Delaware, Inc. v. Pacific Keystone Techs., Inc.*, 326 F.3d 1255, 1264 (Fed. Cir. 2003) ("A basic claim construction canon is that one may not read a limitation into a claim from the written description."). For this reason and those discussed above, Affymetrix's proposed construction should be adopted.

VI. THE PROPER CONSTRUCTION OF THE '365 PATENT

The two disputed terms (with emphasis added) in the '365 patent can be found in claim 1:

> A package for hybridization, comprising:
>
> a substrate comprising a first surface including a probe array with different probes comprising ***biological polymers immobilized on said first surface***;

> said probe array including a density exceeding 100 different biological polymers per cm^2; and
>
> a ***housing*** including a fluid cavity constructed and arranged for hybridization of a target to a probe of said probe array, said housing including a bar code.

(Ex. 9.) The '365 patent claims packages for hybridization and probe arrays at a minimum density with bar codes. Affymetrix proposes the following claim constructions for the disputed terms of the '365 patent.

1. "biological polymers immobilized on a surface"[9]

Affymetrix's proposed construction: "two or more surface-immobilized biological polymers that are recognized by a particular target"

Illumina's proposed construction: "two or more biological polymers of different sequence chemically linked to a single surface"

The meaning of this phrase is clear on its face and no further construction is necessary. Should the Court wish to construe this phrase further, however, the context in which the phrase is used makes its meaning clear. The phrase "biological polymers immobilized on a surface" in the claims of the '365 patent is used synonymously with "probe." That is, it describes the probes that are included in the claimed probe array. For example, claim 1 references "a probe array with different probes comprising biological polymers immobilized on said first surface." Similarly, claim 7 references "a probe array including different probes comprising biological polymers, immobilized on said substrate." Therefore, the proper construction of "biological polymers immobilized on a surface" should be consistent with the definition of "probe" provided in the patent. The '365 patent defines a probe as a "surface-immobilized molecule that is

[9] The claims of the '365 patent include several iterations of this phrase, including "biological polymers immobilized on said first surface" (claim 1), "biological polymers immobilized on said substrate" (claim 7), and "biological polymers, immobilized on a surface" (claim 10). The parties are in agreement that these slightly different phrases have the same meaning.

recognized by a particular target." (Ex. 9, col. 4, lines 4-5.) Accordingly, the phrase should be construed to mean "two or more surface-immobilized biological polymers that are recognized by a particular target."

Illumina appears to agree with this analysis with one caveat – Illumina again tries to manufacture a non-infringement argument by importing the unsupported limitation that the probes be "chemically linked to a single surface." For reasons similar to those discussed in section III.E.1 ("probe array" in the '531 patent), ***supra***, this is incorrect. First, the claims themselves do not support this limitation. The claims require only that the probes be "immobilized" on a "surface" or "substrate." The claims do not discuss "chemically linking" the probes to a "single surface." These omissions should be dispositive. *See Liquid Dynamics Corp. v. Vaughan Co.*, 355 F.3d 1361, 1367 (Fed. Cir. 2004) (noting that the court will look first to the claim language itself when defining the scope of the invention).

Second, the specification discloses probe arrays with ***multiple*** surfaces:

> FIG. 1a illustrates a wafer on which numerous probe arrays are fabricated. The wafer may be composed of a wide range of material, either biological, nonbiological, organic, inorganic, or a combination of any of these, existing as particles, strands, precipitates, gels, sheets, tubing, spheres, containers, capillaries, pads, slices, films, plates, slides, etc. The wafer may have any convenient shape, such as a disc, square, sphere, circle, etc.

(Ex. 9, col. 5, line 62 to col. 6, line 2.) The use of a combination of materials, including, for instance, spheres or particles together with an underlying support, as a substrate for the probe array necessarily means that the probes are not linked to a "single surface" as Illumina would use that term. Therefore, it is clear that the inventors did not intend to limit their invention to the use of probes "chemically linked to a single surface." *See, e.g.*, *Middleton,* 311 F.3d at 1388 (stating that any disavowal of claim scope by the inventor must be clear and unambiguous).

For these reasons, if the Court believes that the phrase "biological polymers immobilized on a surface" needs to be construed, Affymetrix's proposed construction should be adopted.

2. "housing"

Affymetrix's proposed construction: "a structure in which something is contained"

Illumina's proposed construction: "casing that separates the probe array from the atmosphere"

Several of the claims of the '365 patent are directed to packages for hybridization or for supporting a probe array that include a "housing." (Ex. 9, claims 1, 2, 10, and dependent claims.) The term "housing" is not a technical term and has no special meaning in the art. Furthermore, the term does not appear in the '365 patent specification (other than in the abstract). Therefore, "housing" should be interpreted consistently with its widely-accepted meaning: "a structure in which something is contained." *See* Ex. 16, *Random House Webster's Unabridged Dictionary* (1998), at 928 ("anything that covers or protects"); *see also Phillips*, 415 F.3d at 1314 (noting that "general purpose dictionaries may be helpful" when the "ordinary meaning of claim language" is "readily apparent").

The way that the term is used in the asserted claims is consistent with this plain meaning construction. In claims 1 and 2 and their dependent claims, the "housing" includes a "fluid cavity constructed and arranged for hybridization of a target to a probe of said probe array." In other words, the housing contains the probe array during the hybridization process. Similarly, in claim 10 and its dependent claims, the "housing" is "constructed to receive" the chip or probe array. The claims place no other limits on the meaning of "housing."

The '365 patent specification discloses several embodiments of a package to contain a probe array, each with different physical designs, methods for containing the probe array, alignment strategies, and fluid cavities. (Ex. 9, col. 7, line 51 to col. 20, line 28 and associated

figures.) The commonality between them is that each contains the probe array. The inventors expressed no intent to limit their invention to these specific embodiments.

Illumina's proposed construction requires that the "housing" separate "the probe array from the atmosphere." As discussed above, there is no such requirement in the claim language itself. *See Liquid Dynamics*, 355 F.3d at 1367 (looking first to the claim language when construing claim terms). In claim 1, the "housing" need only include a "fluid cavity . . . for hybridization." In claim 2, the "housing" includes a "fluid cavity . . . for hybridization of a target to a probe of said probe array located inside said fluid cavity." The target can be hybridized to the probe array in the fluid cavity regardless of whether the probe array is separated from the atmosphere. Similarly, in claim 10, the "housing" must be "constructed to receive said chip." There is no requirement that the "housing" separate the chip from the atmosphere.

Moreover, it is unclear what Illumina's added limitation would require. Must the casing prevent air from reaching the probe array? How about fluid? Must the casing seal the probe array in a vacuum? The '365 patent specification does not discuss "atmosphere" or "separating" and therefore provides no guidance or support for this limitation.

For each of these reasons, the Court should adopt the plain and ordinary meaning of the term "housing": "a structure in which something is contained."

VII. THE PROPER CONSTRUCTION OF THE '716 PATENT

The disputed terms (with emphasis added) in the '716 patent can be found in claim 1:

> A computer program product that identifies an unknown base in a sample nucleic acid sequence, comprising:
>
> computer code that receives a plurality of signals ***corresponding to probe intensities for a plurality of nucleic acid probes***, each probe intensity ***indicating an extent of hybridization*** of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence, and each nucleic acid probe differing from each other by at least a single base;

> computer code that performs a ***comparison of said plurality of probe intensities to each other***;
>
> computer code that ***generates a base call identifying said unknown base according to results of said comparison and said sequences of said nucleic acid probes***; and
>
> a computer readable medium that stores said computer codes.

(Ex. 10.) The '716 patent claims computer programs and systems for identifying an unknown base in a sample nucleic acid sequence. An example of identifying an unknown base is genotyping, discussed at section II.A., *supra*, where a SNP, or single nucleotide polymorphism, is determined in a sample sequence of DNA. Affymetrix proposes the following claim constructions for the disputed terms of the '716 patent.

1. "probe"

> **Affymetrix's proposed construction:** "a nucleic acid of known sequence that is capable of hybridizing to its complementary sequence"
>
> **Illumina's proposed construction:** "a nucleic acid of known sequence that is capable of hybridizing to a complementary sequence of the unknown sample nucleic acid"

The parties are largely in agreement on the proper construction of the term "probe." Affymetrix and Illumina agree that a "probe" in the '716 patent is "a nucleic acid of known sequence that is capable of hybridizing to its complementary sequence." This construction is consistent with the claim language and the specification. The claims require that the probe have an "intensity" associated with it that indicates "an extent of hybridization of a nucleic acid probe with at least one nucleic acid sequence including said sample sequence." Thus, the probe hybridizes to its complementary sequence. The probes are also *known* sequences because the probes must differ from "each other by at least a single base." These known sequences are used to determine the unknown base in a sample nucleic acid sequence.

The specification uses the term "probe" to mean "a nucleic acid of known sequence that is capable of hybridizing to its complementary sequence." For example, the '716 patent

discusses a set of four probes designed to hybridize to their complementary sequence: "[T]he set of probes differ by only one base so the probes are designed to determine the identity of the base at that position in the nucleic acid sequence." (Ex. 10, col. 6, lines 57-59.) The very purpose of the probe is to hybridize to its complementary sequence.

Illumina's proposed construction is similar to Affymetrix's but adds the requirement that the "complementary sequence" be "of the unknown sample nucleic acid." This limitation is not necessary for a proper construction of the term "probe." The claims of the '716 patent go on to require that each probe has an "intensity" associated with it that indicates "an extent of hybridization of" the probe "with at least one nucleic acid sequence *including said sample sequence*." (Ex. 10, claim 1 (emphasis added).) Therefore, the claims themselves require hybridization of the probes to the sample sequence and Illumina's addition is redundant.

2. "probe intensity"

Affymetrix's proposed construction: "a detectable signal, *e.g.*, fluorescence"

Illumina's proposed construction: "intensity from a labeled sample nucleic acid hybridized to a probe location"

In the claims of the '716 patent, computer code receives "signals" corresponding to "probe intensities," each of which indicates "an extent of hybridization" of a probe "with at least one nucleic acid sequence including said sample sequence." Thus, the "probe intensity" is a signal that indicates the "extent of hybridization." Based on the claims themselves, the proper construction of the term "probe intensity" is "a detectable signal." The specification confirms this construction and provides examples of such "detectable signals."

The specification uses the term "fluorescence intensities" as synonymous with "probe intensities." (Ex. 10, col. 22, lines 11-12 ("Based upon an analysis of the fluorescence intensities and locations, it becomes possible to extract information such as the monomer sequence of DNA

or RNA.").) The specification references "probe intensity" several times. (*See, e.g.*, Ex. 10, col. 11, lines 38-39; col. 23, line 23; col. 24, line 7; col. 25, line 27-28.) In each of these instances, "probe intensity" refers to the amount of signal relating to a probe. The purpose of the "probe intensity" is to provide a signal to the computer program that "indicates an extent of hybridization" of the probe with some sequence.

The specification discloses various types of detectable signals used on probes – for example, fluorescent markers and distinguishable radioactive markers. (Ex. 10, col. 21, lines 39-44.) The signal used most prevalently throughout the specification is fluorescence. Claim 10 of the '716 patent – which adds the requirement that the "plurality of probe intensities are fluorescent intensities" – confirms that the "probe intensity" of claim 1 can be fluorescence, but is not limited to fluorescence. *See Phillips*, 415 F.3d at 1314 ("Differences among claims can also be a useful guide in understanding the meaning of particular claim terms."). Thus, the proper construction of "probe intensity" is "a detectable signal, ***e.g.***, fluorescence."

Illumina's proposed construction is an attempt to import one of its non-infringement arguments into the claim construction process. Specifically, Illumina would limit the term "probe intensity" to "intensity ***from a labeled sample nucleic acid***." The claims of the '716 patent are not so limited. They require only a "probe intensity" that indicates "an extent of hybridization." The claims do not discuss labeling the sample nucleic acid. In fact, they place no limitations on where the probe intensity comes from or how it is generated, so long as it indicates an extent of hybridization. There could not be a clearer example of adding a limitation – labeling the sample nucleic acid – that does not appear in the claims.

In fact, there are many ways for a "probe intensity" to indicate that the probe has hybridized. One way is to label the sequence that hybridizes to the probe. But equally effective ways are to label the probe or the hybrid after hybridization. Each of these methods can be used

to determine which probe has hybridized to a target. There is nothing in the claim language of the '716 patent that would exclude labeling the probe or the hybrid, as opposed to the sequence hybridized to the probe, to create the "probe intensity" indicating an extent of hybridization.

Illumina's proposed construction is a classic case of importing limitations from the specification into the claims. *See CollegeNet*, 418 F.3d at 1231 ("In examining the specification for proper context, however, this court will not at any time import limitations from the specification into the claims."). Examples in the '716 patent specification describe "probe intensities" arising from a labeled sample nucleic acid, but there is no indication that the inventors intended to limit their invention to those embodiments. (Ex. 10, col. 26, lines 52-63 (expressing intent not to limit invention to the disclosed examples).) Indeed, the broad claim language is inconsistent with any such inference.

For the same reasons, Illumina's attempt to include the limitation of "a probe location" into the construction of "probe intensity" should be rejected. The requirement that the probes have a "location" appears nowhere in claims 1, 2, 5, 6, or 10. All that is required is that the computer code receive signals corresponding to probe intensities, perform a comparison of those intensities, and generate a base call. One common way to obtain the intensity data is to associate the probe at some point in the assay with a particular location. It is not necessary, however, for the probes to have a specific location associated with them – they could be in solution, immobilized on a support, or otherwise.

Claim 9 of the '716 patent (which depends from claims 5, 6, 7, or 8) confirms that "probe intensity" should not be limited to a "probe location." Claim 9, unlike claims 1, 2, 5, 6, and 10, requires that "the plurality of nucleic acid probes are in an array of probes." As we have seen, an "array of probes" has probes at particular locations. Because claim 9 adds an additional limitation, there is a presumption that the limitation is not present in the independent claims. *See*

Phillips, 415 F.3d at 1314-15 ("[T]he presence of a dependent claim that adds a particular limitation gives rise to a presumption that the limitation in question is not present in the independent claim."). Therefore, Illumina's construction of "probe intensity" as requiring a "probe location" is not supported by the claims themselves.

3. "corresponding to probe intensities for a plurality of nucleic acid probes"

Affymetrix's proposed construction: "relating to a detectable signal, *e.g.*, fluorescence, from two or more nucleic acid sequences of known sequence that are capable of hybridizing to a complementary sequence"

Illumina's proposed construction: "two or more probe locations each having one and only one probe intensity"

The claims of the '716 patent require that the computer code receive a plurality of signals "corresponding to probe intensities for a plurality of nucleic acid probes." The proper construction of this phrase incorporates the constructions of "probe intensities" and "probes" discussed above. "Corresponding to" has its ordinary meaning of "relating to." The parties have agreed that "plurality" means "two or more." Therefore, taken together, the phrase should be interpreted to mean "relating to a detectable signal, *e.g.*, fluorescence, from two or more nucleic acid sequences of known sequence that are capable of hybridizing to a complementary sequence."

Illumina's proposed construction repeats the error discussed above – requiring the "probe intensity" to have a "probe location" – and should be rejected for the same reason. Illumina would also require each "probe location" to have "one and only one probe intensity." This additional limitation is also not supported by the intrinsic evidence.

First, there is no requirement in the claims that an intensity even have a location; thus, it makes no sense to require that each probe location have only one associated probe intensity. Second, the claims require that the computer code receive a "plurality of signals" corresponding

to probe intensities. This language does not impose limits on the number of probe intensities, so long as there is a "plurality," two or more. Third, the specification provides an example, the "Pooling Processing" method, where more than one probe intensity is obtained from a location. (Ex. 10, col. 21, line 35 to col. 22, line 21.) In that example, a reference sequence and a sample sequence are labeled "with different fluorescent markers emitting light at different wavelengths" (in other words, two different colors) and then hybridized to an array. Either or both (or neither) sequence may hybridize to any particular location and either or both colors may be detected at a single location. Illumina's construction adds an additional limitation – each "probe location" having only "one probe intensity" – that would exclude this disclosed embodiment. *See Pfizer*, 429 F.3d at 1374. Therefore, Illumina's proposed construction of the phrase is flawed.

4. "indicating an extent of hybridization"

Affymetrix's proposed construction: "relating to the relative binding of"

Illumina's proposed construction: "indicating the strength of binding so as to distinguish a single-base mismatch"

In the claims of the '716 patent, each probe intensity "indicat[es] an extent of hybridization." The phrase "indicating an extent of hybridization" should be construed according to its plain and ordinary meaning as it has no special meaning in the art. "Indicating" should be defined consistent with its normal usage: "relating to." An "extent of hybridization" in the context of the '716 patent connotes a degree or relative amount of binding[10] – that is, measured against another binding event. *See* Ex. 17, *Random House Webster's Unabridged Dictionary* (1998), at 684 (defining "extent" as the "degree to which a thing extends"). The specification consistently discusses "probe intensities" – each of which indicates "an extent of hybridization" – in relation to one another. (*See, e.g.*, Ex. 10, col. 11, lines 39-64 (comparing the

[10] Both parties agree that "hybridization" means "binding" in the '716 patent claims.

probe intensities of four probes to one another).) The probe intensities have no meaning standing alone – they are only meaningful when compared against other probe intensities. Thus, the probe intensity indicates the relative – not absolute – binding of the probe.

The phrase "indicating an extent of hybridization" says nothing about the purpose of the indication or what the indication will be used for. Nevertheless, Illumina would build just such a limitation into the phrase by including "so as to distinguish a single-base mismatch" in the construction. Nothing in the claims supports the inclusion of a purpose requirement into a purely descriptive phrase, "indicating an extent of hybridization." Indeed, the claims themselves go on to describe the purpose of the probe intensities – they are compared against one another to "generate[] a base call identifying said unknown base." Illumina's attempt to redefine the purpose of the probe intensity through construction should be rejected.

5. "comparison of said plurality of probe intensities to each other"

Affymetrix's proposed construction: "an examination of the detectable signals of two or more probes in relation to each other"

Illumina's proposed construction: "ranking of probe intensities from a hybridization experiment"

The phrase "comparison of said plurality of probe intensities to each other" should be interpreted according to its plain and ordinary meaning. A "comparison" of two or more things is an examination of those things in relation to each other. *See* Ex. 18, *Random House Webster's Unabridged Dictionary* (1998), at 416 (defining "compare" as "to examine . . . in order to note similarities and differences"). As we have seen, a "probe intensity" is a "detectable signal" and a "plurality" is "two or more." Therefore, "a comparison of said plurality of probe intensities to each other" should be defined as "an examination of the detectable signals of two or more probes in relation to each other."

This plain meaning definition is consistent with the '716 patent's specification. The patent describes many types of "comparisons" of probe intensities: for example, the intensity ratio method (Ex. 10, col. 7, line 34 to col. 10, line 39), the reference method (Ex. 10, col. 10, line 40 to col. 17, line 44), and the statistical method (Ex. 10, col. 17, line 45 to col. 22, line 21). Each of these methods examines the detectable signals from two or more probes in relation to each other. Neither the claims nor the specification of the '716 patent place limits on the particular type of comparison to be performed.

Illumina's proposed construction does just that – limiting the "comparison" to "***ranking*** of probe intensities from a hybridization experiment." Nothing in the claims suggests that a "comparison" is limited to a "ranking." *See Liquid Dynamics*, 355 F.3d at 1367 (looking first to the claim language when construing claim terms). Indeed, the terms "rank" or "ranking" do not appear in the '716 patent.

The specification describes comparisons ***other than*** ranking of probe intensities. As one example, in the intensity ratio method, each probe intensity is measured against each other probe intensity to calculate a ratio. (Ex. 10, col. 9, lines 2-13.) The unknown base is then determined by whether the ratio exceeds a predetermined ratio cutoff. There is no need to "rank" the probe intensities in this comparison. A similar comparison is performed in the reference method. (Ex. 10, col. 12, lines 53-65.) Thus, Illumina's proposed construction – which would limit the "comparison" of probe intensities to a "ranking" – is inconsistent with the patent specification. Illumina's attempt to pull limitations from select portions of the specification into the claims should be rejected.

6. "generates a base call identifying said unknown base"

Affymetrix's proposed construction: "determines which nucleotide is most likely to be present at a particular position in a nucleic acid sequence"

Illumina's proposed construction: "identifies a nucleotide as A, C, T, or G"

The computer program claimed in the '716 patent includes computer code that "generates a base call identifying said unknown base." The parties appear to be largely in agreement about the proper construction of this term. A "base call" is a determination of the identity of a base, or nucleotide. (Ex. 10, col. 25, lines 9-15 (equating "calling the base" with determining which nucleotide is present at a location in the sequence of interest).) The specification makes clear that the "base call" is not an absolute identification of a nucleotide, but rather a prediction of the identity of the nucleotide most likely to be present. (Ex. 10, col. 15, lines 3-6 (discussing an improved method "resulting in more accurate base calling"); col. 21, lines 32-33 ("The statistical method has also been used to implement confidence estimates . . . ."); col. 13, lines 23-47 (assigning confidence codes to the "base call").)

The "unknown base" that is determined is the base in the sample nucleic acid sequence. The "unknown base" must be at a specific position in that sequence for its identity to be determined. For example, the reference method discussed in the specification requires a reference sequence (which has a previously known sequence). (Ex. 10, col. 10, line 40 to col.17, line 44.) The method compares the hybridization intensities from probes hybridized to the sample sequence to intensities from probes hybridized to the reference. Those probes include sets of probes that are designed to interrogate specific positions in the reference sequence that correspond to interrogation positions in the sample sequence. Thus, the reference method requires that the position of the base being determined in the nucleic acid sample (*i.e.*, the unknown base) is known. The other methods discussed in the specification – for example, the intensity ratio method and the statistical method – similarly assume that the position of the unknown base in the sample sequence is known.

Affymetrix's proposed construction – "determines which nucleotide is most likely to be present at a particular position in a nucleic acid sequence" – is therefore consistent with the plain meaning of the phrase and the intrinsic evidence. Illumina's proposed construction is not as accurate as Affymetrix's. First, it fails to include the idea that the determination or identification need not be absolute – the "base call" is a prediction of which base is most likely to be present. Second, it fails to convey that the unknown base is at a particular and known position in the sample sequence. Affymetrix's proposed construction is preferable for these reasons.

7. "generates a base call . . . according to results of said comparison and said sequences of said nucleic acid probes"

Affymetrix's proposed construction: This phrase should be construed consistently with Affymetrix's above proposed constructions

Illumina's proposed construction: "generates a base call as the base-pair complement to the probe with the highest probe intensity"

Based on the constructions proposed above, this phrase – which is a collection of several of the phrases and terms already construed – need not be further construed. Affymetrix stands by its proposed constructions of "generates a base call identifying said unknown base," "comparison," and "probe."

Illumina's proposed construction once again attempts to limit the claims of the '716 patent to one type of comparison – a ranking of probe intensities. According to Illumina's construction, the base call is made solely based on which probe has the highest probe intensity. As discussed above, however, the patent discloses several types of "comparisons," including methods other than ranking probe intensities. Moreover, the claims themselves do not require making a base call based on which probe has the highest probe intensity – rather, the base call is made based on the results of the "comparison," whatever form that comparison may take.

Therefore, Illumina's proposed construction is not supported by the claims or the specification of the '716 patent.

CONCLUSION

For the foregoing reasons, the Court should adopt Affymetrix's proposed claim construction for the patents-in-suit.

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CERTIFICATE OF SERVICE

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